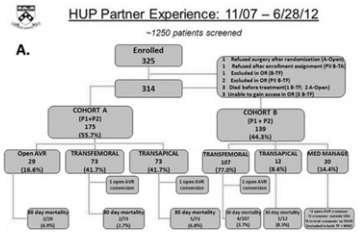
developed to streamline patient screening, study enrollment and ensure patient follow up. Patient care protocols and specific study instructions were developed and distributed to all healthcare providers. The TAVR research model proved to be a excellent platform for management of a complex clinical trial and was used as a template for the transition to a commercial TAVR program.



B.	Baseline	During procedure	Day 1	Discharge	30 Day	6 Month	12 Month	Annual Visit
Informed Consent	X							
History	X							
Physical Exam	X			X	X	X	X	X
NYHA Class	X			X	X	X	X	X
Adverse Event Assessment	X	X		X	X	X	X	X
Neurological Exams/Assessment	X			X	X	X	X	X
Risk Scoring	X							
Six Minute Walk Test	X				X	X	X	
Frailty Studies	X							
Laboratory Studies	X		X	X	X	X	X	X
Non-Invasive Tests	X		X	X	X	X	X	X
Invasive Tests	X	X				X		
Quality of Life Measures	X				X	X	X	X

SCIENCE

Angiomyogenesis, Cell Therapy, Gene Therapy

CRT-111

Hypoxia Reoxygenation-induced Myocardial Cell Apoptosis Can Be Rescued By Frizzled-2 Suppression

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Background: This study is aiming to find the signal transduction underlying calcium overloading caused cell apoptosis phenomenon post myocardial treatments.
Methods: For the information of Wnt5a/frizzled-2 signal pathway in mammalian cardiac cells were hardly seen before, first we needed to confirm the gene and protein expression of the effectors (wnt5a;frizzle-2;p-camkii, the marker presents the activation of this signal) which consisting this signal within myocardial cells, through q-rtpcr, western blot and some specific methods in detail.

Second, we transfected the cells with frizzled-2 gene in order to activate this pathway, and recorded the intracellular and cellular effects like cell apoptosis. Third, we used Stealth RNAi to conduct frizzled-2 gene suppression, then observed the following effects. Results indicated the role of Wnt5a/Frizzled-2 pathway played in calcium overloading process and cell apoptosis. Next, we analyzed the expression of the effectors of this pathway after the cells were conducted through hypoxia/reoxygenation treatment. In this part, the same testing objects and methods were used to consistent with different treatment groups.
Results: First, results from simple cell interference test showed that wnta5a, frizzled-2 and p-camkii is stable expressing in cardiac cells.

Second, High expression of p-CamkII followed by intracellular accumulation of calcium post frizzled-2 transfection indicates the activation of wnt5a/Frizzled-2 pathway. This was proved by gene suppression of frizzled-2 on the membrane: down regulation of frizzled-2 gene caused down expression of Frizzled-2 protein and p-CamkII marker, also the calcium accumulation and apoptosis.

Third, data from hypoxia/reoxygenation treatment group is found have the same trend echoes to part 1. Whatever in hypoxia group or in reoxygenation group, expression of Frizzled-2 on the cell membrane determines the character of wnt5a and downstream effectors, and eventually affects the intracellular calcium accumulation and apoptosis.
Conclusion: We hypothesis that activation of wnt5a/Frizzled-2 pathway post myocardial treatments could be a main reason causing calcium overloading and cell apoptosis. Results have proved our hypothesis, and this is the first paper in this area in evaluating this signal pathway within mammalian cardiac cells and raising a possible concept that activation of this signal pathway might be one of the mechanisms underlying cell apoptosis post myocardial treatments.

CRT-112

Exendin-4 Improves the Survival and Therapeutic Efficacy of Implanted Stem Cells Following Myocardial Infarction

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Background: The poor survival rate of stem cell transplantation in ischemic myocardial microenvironment is a major obstacle for stem cell therapy. Exendin-4 holds the potential of cardioprotective effect based on their pleiotropic activity. This study was designed to investigate whether the combination of Exendin-4 and adipose derived stem cells (ADSCs) could significantly improve the stem cells survival, engraftment and contribute to myocardial repair after myocardial infarction.
Material and Methods: The oxidative stress of cultured ADSCs was induced by H2O2 administration in vitro. The protective effect of Exendin-4 was investigated by dihydroethidium (DHE) staining and Live/Dead assay. For in vivo studies, MI was induced by the left anterior descending artery ligation in adult male Sprague-Dawley rats. ADSCs carrying dual-fusion (TF) reporter gene (fluc-mrfp) were quickly injected into border zone of myocardial infarction in rats treated with or without Exendin-4. PBS alone was injected as control. Multi-techniques were used to assess the beneficial effects after transplantation.
Results: The results showed that exendin-4 decreased ros level and reduced the necrosis of adscs suffered from oxidative stress significantly in vitro. one week after transplantation, inflammatory cells and oxidative stress of heart in exendin-4 group were decreased markedly than that in control group. four weeks after transplantation, the cardiac function evaluated by echocardiogram and MicroPET/ct improved significantly, while the infarct size and fibrotic area decreased significantly in Exendin-4+adscs group compared with that of other groups. both exendin-4 group and adscs group also improved myocardial performance. bioluminescence imaging showed exendin-4 promoted adscs survival significantly in vivo. histology examination showed that the combination of exendin-4 and adscs could reduce myocardial fibrosis, decrease myocardial apoptosis, increase vessel density, and enhance cardiogenic differentiation of adscs. western blotting demonstrated that oxidative stress and inflammation were significantly inhibited in the border area of infarction in Exendin-4+adscs group.
Conclusion: Through regulating the post-infarct microenvironment, exendin-4 combined with adscs can improve the survival and therapeutic efficacy of implanted stem cells. this study suggests the potential of exendin-4 for stem cell based heart regeneration.

Atherosclerosis

CRT-113

A Reproducible Animal Model of Calcified Atherosclerotic Plaque from a Cylindrical Bone Marrow Allograft Implanted in the Porcine Coronary and Peripheral Vasculature

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A reproducible animal model of calcified atherosclerotic plaque exhibiting properties similar to those observed in the human population has proven difficult to develop. We therefore investigated the use of a bone marrow plug, placed interventionally in the

coronary and peripheral arteries, to simulate the properties of a calcific chronic partial occlusion (CPO) lesion for the evaluation of catheter based technologies.

Forty-one pigs were prepped sterilely for creation of the CPO. An introducer sheath was placed in the carotid artery for vascular access. Angiograms of the left anterior descending (LAD) coronary artery and the iliac tree were obtained. A section of artery measuring 2.8 - 3.0mm in diameter was identified and targeted for implantation with the plug. A cylinder of bone marrow measuring 3mm in outer diameter by 10mm in length was obtained from the rib of a donor animal and a lumen measuring approximately 1.6mm in diameter was created. The bone plug was loaded into a 9Fr guide catheter, tracked to the targeted location within the artery and deployed. Angiography immediately post deployment demonstrated an average lesion lumen diameter of 1.32mm (1.08 - 2.35mm).

Twenty-nine of forty-one pigs (implanted with a total of thirty-five bone plugs) survived to the scheduled follow-up procedure (between 4 and 14 days). Thirty of the thirty-five surviving implanted bone plugs were patent, with follow-up angiography demonstrating reduced blood flow through the lesion, with an average lesion lumen diameter of 1.20mm (0 - 2.59mm).

We can reliably create a porcine coronary model simulating a calcific partial occlusion, which can be used for the evaluation of interventional technologies and platforms used to treat coronary and peripheral artery disease. The results of previous studies have demonstrated successful deployment of a chronic total occlusion (CTO) version of the bone plug in the coronary and peripheral vasculature. Additionally, we have successfully implanted larger bone marrow plugs (measuring 3.0 - 5.5mm in outer diameter) and demonstrated the ability to reduce the calcium content of the bone marrow plug prior to deployment, thereby decreasing the hardness of the lesion.

CRT-114

Correlation Between Carotid Ultrasonographic Parameters And Syntax Score According To The Extent Of Coronary Artery Disease

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Background: Carotid ultrasonography is a good non-invasive modality to evaluate atherosclerotic changes. Intima-media thickness (IMT) is a well-established surrogate marker of coronary atherosclerosis. But, the role of other carotid parameters for predicting coronary artery disease (CAD) is still lack of evidence. Therefore, we evaluated the correlation between carotid parameters and SYNTAX score (SS) representing the severity and extent of CAD. We also investigated whether carotid parameters predict the presence of CAD or not.

Methods: Total 663 of 1698 patients (408 men, mean age: 64.1 ± 11.9 years) who performed both carotid ultrasonography and coronary angiography during admission from Sep 2011 to Aug 2012 were studied. The patients were divided into three groups: normal or minimal CAD, 1 vessel disease (VD) and ≥2VD. Plaque score (PS) was defined as a numerical summation of the presence of plaque in 4 different locations of both carotid arteries. Maximum % diameter stenosis (DS) and area stenosis (AS) were measured at the narrowest portion in longitudinal and short axis view.

Results: The old age, male gender, diabetes mellitus and smoking were significantly related to the extent of CAD. All carotid parameters showed significant relationship with the extent of CAD. Mean carotid IMT, maximum carotid IMT, PS, %AS and %DS were weakly but significantly correlated with SS (r=0.226, 0.162, 0.336, 0.361, 0.318, respectively, all p value < 0.001). After adjusted for classic risk factors, PS was the best predictor for CAD (Odds ratio 1.576, 95% confidence interval 1.365-1.820, p<0.001). The diagnostic accuracy of PS for the detection of CAD by the area under the receiver operating characteristics curve was 0.702 (95% confidence interval 0.661-0.743, p<0.001).

Conclusion: All carotid parameters were weakly but significantly correlated with SYNTAX score. PS was a good predictor for coronary artery disease. Long-term follow-up is warranted to discriminate clinical outcomes using carotid ultrasonographic parameters.

Other

CRT-115

Demographics Of Study Participants In Clinical Trials For Cardiovascular Drugs Approved By FDA From 2010 To 2011

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Objectives: Historically, women and minorities have been underrepresented in clinical trials of drugs to treat cardiovascular disease (CVD). To accurately assess the safety and efficacy of CVD drugs, the U.S. Food and Drug Administration (FDA) has made a conscious effort to ensure adequate representation of women and minorities in clinical drug trials through guidance documents and regulations. The purpose of this study is to assess the participation of women and racial/ethnic minorities in FDA-reviewed CVD drug trials that were included in New Drug Applications (NDAs) approved between 2010 and 2011.

Methods: The sex and race/ethnicity of subjects in all CVD drug clinical trials submitted to FDA in support of NDAs approved between January 2010 and December 2011 were assessed from final clinical study reports. The reports were accessed via internal FDA databases.

Results: Four drugs (1 per NDA) indicated for hypertension (HTN), acute coronary syndrome (ACS), non-valvular atrial fibrillation (NAF) and deep vein thrombosis/pulmonary embolism (DVT/PE) after joint replacement surgery were approved during the period studied. A total of 231 clinical trials classified as phase 1, 2, or 3 studies were submitted to the NDAs. There were 107,156 subjects included in these studies. Demographic analysis (shown in Table 1) indicated that the mean participation of women in these trials was 41% and the majority of the trial subjects were Caucasians (79%). When analyzed by the phase of the trials, mean female participation was 21%, 43% and 42% for Phase 1, 2 and 3 respectively.

Table 1. Subject Demographics in CVD drug trials of NDAs approved by FDA from 2010 to 2011.

	Overall N=107156	HTN N=10558	ACS N=21127	NAF N=33662	DVT/PE N=41809
Sex					
Females N (%)	44169 (41)	4643 (44)	5960 (28)	13960 (41)	19606 (47)
Males N (%)	62987 (59)	5915 (56)	15167 (72)	19702 (59)	22203 (53)
Race					
Caucasian N (%)	84587 (79)	7201 (68)	18942 (90)	26291 (78)	32153 (77)
Black N (%)	2571 (2.4)	1254 (12)	462 (2.0)	228 (6.8)	627 (1.5)
Asian N (%)	9077 (8.5)	1058 (10)	1321 (6.3)	1085 (3.2)	5613 (13)
Hispanic* N (%)	1969 (1.8)	1119 (11)	66 (3.1)	0	784 (1.9)
Other** N (%)	2242 (2.1)	1027 (9.7)	343 (1.6)	159 (0.5)	713 (1.7)
Unknown^ N (%)	2111 (2.0)	0	0	466 (1.4)	1645 (3.9)

*Depending on the study, Hispanic subjects were counted either as Caucasian or a separate race/ethnicity category. **Includes those classified as American Indian/Alaska Native, Hawaiian/Pacific Islander, Multiracial or Other. ^Any participants whose race is listed as missing or who participated in studies where there were legal concerns about collecting race data (applied in some European trials).

Conclusions: The overall inclusion of women in these CVD drug trials is comparable to the overall female CVD population (51%) in the US. However, women are largely underrepresented in the Phase 1 trials, during which much of the pharmacokinetics and pharmacodynamics of new drugs are evaluated.